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NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/589,677	ONICHTCHOUK, DARIA	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *July 7, 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *23-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 August 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *October 6, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restrictions

Applicant's response to the Requirement for Restriction, filed on July 7, 2008 is acknowledged.

Applicant has elected the invention of Group V, claims 1-22, drawn to a pharmaceutical composition comprising a SF01, SF02, SF03, SF04, SF05, SF06, SF07, SF08, SF09, SF10, SF11, SF12 or SF13 protein, or functional fragment thereof, and a nucleic acid molecule encoding a SF01, SF02, SF03, SF04, SF05, SF06, SF07, SF08, SF09, SF10, SF11, SF12 or SF13 protein or a functional fragment thereof.

Within Group V, Applicant has further elected the restricted subgroup "SF06".

Election of Applicant's invention(s) was made without traverse. Because Applicant did not distinctly and specifically point out the supposed errors in the Group or species restriction requirement, the election has been treated as an election without traverse and the restriction and election requirement is deemed proper and therefore made final (MPEP § 818).

This application contains claims drawn to non-elected inventions, specifically SF01, SF02, SF03, SF04, SF05, SF07, SF08, SF09, SF10, SF11, SF12 and SF13 proteins and nucleic acids, and effector/modulator of said nucleic acids and/or proteins. Furthermore, claim 11 recites an improper Markush group that is not compliant with *In re Harnisch*, wherein the polynucleotide may be a probe, primer or anti-sense oligonucleotide. Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility. However, those of ordinary skill in the art recognize that neither primers nor anti-sense nucleic acid encode polypeptides. Thus, absent evidence to the contrary, the recitation of such primers and anti-sense molecules are structurally and functionally distinct from the elected nucleic acid of claim 1 required to encode a SF06 polypeptide.

A complete reply to this Office Action must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 23-42 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-22 are under consideration.

Priority

This application is a 371 of PCT/EP05/01711 filed on February 18, 2005. Applicant's claim for the benefit of the prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). An English translation of the foreign patent application EPO 04003914.1 filed on February 20, 2004 and the certified copy has been filed with the instant application.

Accordingly, the effective priority date of the instant application is granted as February 20, 2004.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on October 6, 2006. The Examiner was able to consider these to the extent of time allowable. The signed and initialed PTO Forms 1449 are mailed with this action.

Drawings

1. **The drawings are objected to because** the figure legend of Figure 2A (papers filed August 16, 2006) is truncated. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the

remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the Examiner, the Applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

2. **The disclosure is objected to because of the following informalities:**

The "99,6%" should be "99.6%" (pg 9, line 1).

It appears that a symbol formatting error has occurred regarding the 4?20% (pg 39, line 21).

Appropriate correction is required.

Claim Objections

3. **Claims 12-22 are objected to under 37 CFR 1.75(c),** as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The instant invention (claim 1) is a pharmaceutical composition comprising a SF06 protein and a nucleic acid encoding a SF06 protein. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. However, claims 12-22 recite different intended uses of the inventive pharmaceutical composition. The intended use limitations do not contain any further structural limitations with respect to claimed pharmaceutical composition of claim 1. See MPEP §2114.

4. **Claims 4, 7-9 and 11 are objected to because of the following informalities:**

As a first matter, the claim does not end in a period. While there is no set statutory form for claims, the present Office practice is to insist that each claim must be the object of a sentence starting with "I (or we) claim," "The invention claimed is" (or the equivalent). Each claim begins with a capital letter and ends with a period. Periods may not be used elsewhere in the claims except for abbreviations. See *Fressola v. Manbeck*, 36 USPQ2d 1211 (D.D.C. 1995). Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation. See 37 CFR 1.75(i).

As a second matter, the use of Markush-type language "selected from the group consisting of (a), (b), (c), (d), (e), (f)" is incorrect. Rather, the Markush-type language should be "selected from the group consisting of (a), (b), (c), (d), (e) **and** [*emphasis added*] (f). See MPEP §803.02. It would be remedial to insert the conjunction "and" between embodiments (e) and (f).

As a third matter, the phrase "with as" (part (c), line 1) is incorrect grammar because the recitation fails to identify the object/product to which the comparison "with as" is made.

As a fourth matter, the term "99,6%" (part (e), line 3) should be "99.6%".

With respect to claims 7-8, the claims recites a polynucleotide encoding a SF06 polypeptide, and a vector comprising said polynucleotide, wherein the intended used of the polynucleotide is for gene therapy. However, those of ordinary skill in the art recognize that a polynucleotide encoding a SF06 polypeptide will not, in and of itself, express SF06. Rather, said polynucleotide requires additional *cis*-acting elements to promote the transcription and/or translation of said polynucleotide, wherein such required *cis*-acting elements in combination with said polynucleotide are commonly known in the art as "vectors". Furthermore, "In molecular biology and genetic engineering a **vector** is a vehicle for transferring genetic material into a cell." (www.answers.com/topic/vector-biology; last visited August 5, 2008). Thus, in light of the recited use of the polynucleotide for gene therapy for transferring genetic material into a cell, and the art-recognized definition of a "vector", the recitation of "a vector, particularly an expression vector" is redundant with, and fails to further limit the polynucleotide of claim 1 because the polynucleotide of claim 1 is inherently a vector, absent evidence to the contrary. It logically follows that the nucleic acid molecule is inherently recombinant.

With respect to claim 9, the recitation "wherein the polypeptide is a recombinant polypeptide" is redundant with the SF06 polypeptide of claim 1, absent evidence to the contrary. What are the structural features of a recombinant SF06 polypeptide that would clearly distinguish it from a non-recombinant SF06 polypeptide?

With respect to claim 11, the claim recites an improper Markush group that is not compliant with *In re Harnisch*, wherein the polynucleotide may be a probe, primer or anti-sense oligonucleotide. Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility. However, those of ordinary skill in the art recognize that neither primers nor anti-sense nucleic acid encode polypeptides, and thus the recitation of such molecules are structurally and functionally distinct from the elected nucleic acid of claim 1 required to encode a SF06 polypeptide.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

5. **Claims 4, 8 and 16 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

With respect to claim 4, the claim recites (parts (a) and (b)) a nucleic acid molecule or a protein "as shown in Table 2". However, Table 2 annotates database accession numbers corresponding to given SF products. At issue is that the database is subject to continuous updates and corrections, and thus nucleic acid sequence and amino acid sequence of the claimed molecules may change over time. Thus, the claims are indefinite for failing to recite the reference sequences at the time of filing the instant application.

With respect to claim 4, the claim is indefinite in the recitation of the term "preferably" (part (e)). It is unclear whether any of the limitations which follow the term "preferably" are required limitations. Therefore the metes and bounds of this claim are unclear. It is unclear how the artisan's preference would or would not infringe upon the claimed invention because preferences are subjective cognitive perspectives.

With respect to claims 8 and 16, the claims are indefinite in the recitation of the term "particularly". It is unclear whether any of the limitations which follow the term "particularly" are required limitations. Therefore the metes and bounds of the claims are unclear.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. **Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.** The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a pharmaceutical composition comprising a SF06 protein or functional fragment thereof and a nucleic acid encoding a SF06 protein. At issue for the purpose of written description requirements is the lack of adequate support for the enormous genus of functional SF06 polypeptide variants and fragments.

> *Vas-cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written

description' inquiry, whatever is now claimed." (See page 1117.) The specification should "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see *In re Shokal* 113USPQ283(CCPA1957); *Purdue Pharma L.P. vs Faulding Inc.* 56 USPQ2nd 1481 (CAFC 2000). To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, SF06 is the only species whose complete structure is disclosed.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other identifying characteristic is that the SF06 variant or fragment would be functional.

Applicant has found that SF06 (also known in the art as Cerebellin 2 (Cbln2)) is expressed in the pancreas (pg 11, lines 10-11; Figure 8). The prior art recognizes that Cbln2 exerts a neuromodulatory function and thus are useful as a class of transneuronal regulators of synapse development and synaptic plasticity in various regions of the brain. However, the prior art is silent regarding SF06/Cbln2, or variants or fragments thereof, for the treatment of pancreatic diseases (e.g. diabetes mellitus, such as insulin dependent diabetes mellitus and/or non insulin dependent diabetes mellitus), obesity, metabolic syndrome, eating disorder, cachexia, hypertension, coronary heart disease, hypercholesterolemia (dyslipidemia), and/or gallstones, as

contemplated by Applicant. The specification discloses no examples regarding which amino acids may be altered in the reference SF06 amino acid sequence so as to retain functionality so as to be useful in a therapeutic pharmaceutical composition to treat an enormous genus of etiologically and pathologically distinct diseases and/or disorders. The specification does not disclose any identifying characteristic as to how an artisan would have assayed functionality of the SF06 polypeptide variants. It is noted that all these SF06 amino acid variants and fragments vary greatly in structure and function and therefore each represents a subgenus. Again, the members of any of the subgenuses themselves would have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenuses.

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (col. 3, page 71434), "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (col. 2, page 71436).

An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998),

Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. *In Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *See Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function … does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is").

The Applicant has not provided any description or reduction to practice of a functional SF06 amino acid variant or fragment useful as a pharmaceutical composition to treat an enormous genus of etiologically and pathologically distinct diseases and/or disorders. Based on the Applicant's specification, the skilled artisan cannot envision the detailed chemical structure of a functional SF06 amino acid variant or fragment encompassed by the claims. The one species of agent specifically disclosed, SF06, is not representative of the genus because the genus is highly variant.

Accordingly, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the Applicant is in possession of the broad genus of functional SF06 amino acid variants or fragments, besides SF06, at the time the application was filed.

Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

7. **Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

Applicant claims a pharmaceutical composition comprising an enormous genus of SF06 proteins or functional variants thereof, and a nucleic acid encoding said enormous genus of SF06 proteins or functional variants thereof, and thus the claimed subject matter is within the realm of protein therapy and gene therapy for the treatment of an exceptionally enormous genus of etiologically and pathologically distinct medical conditions, including an enormous genus of

etiologically and pathologically distinct cell proliferative disorder (reading on any cancer) in an enormous genus of animals as per *in vitro*, *ex vivo* or *in vivo* therapy methods.

The nature of the invention involves one of the most complex and unpredictable areas of medicine molecular biology - gene therapy treatment of cancer and/or diabetes. Applicant contemplates the *in vivo*, viral and non-viral expression vectors to treat a condition in need of treatment (pg 13, lines 28-37). As such, the as-filed specification attempts to claim that any of the disclosed vectors, and regardless of the nature of the claimed heterologous nucleic acid, can be employed as a master drug to treat any disorder.

At issue is the lack of enabling support in the specification to guide the artisan how to make and use the enormous genus of SF06 proteins or functional variants thereof for the treatment, alleviation and/or prevention of pancreatic diseases such as diabetes, obesity, and other metabolic syndromes, and/or modulating pancreatic development and regenerating pancreatic tissues or cells.

The Existence of Working Examples, The Amount of Direction Provided by the Inventor, and The State of the Prior Art

This invention relates to the use of secreted SFOI-SF13 proteins, to the use of polynucleotides encoding these, and to the use of effectors/modulators thereof in the diagnosis, study, prevention, and treatment of pancreatic diseases (e.g. diabetes mellitus), obesity and/or metabolic syndrome and to the use in regeneration of tissues such as pancreatic tissues and others (pg 1, ¶1). More specifically, the invention relates to the identification of candidate genes that are specifically expressed in early development in certain pancreatic tissues. These genes and the thereby encoded proteins can provide tools to the diagnosis and treatment of severe pancreatic disorders and related diseases (pg 5, lines 10-13).

The specification discloses that SF06 is secreted by brain, adrenal cortex and adrenocortical tumors. SF06 is involved in the regulation of steroid hormone secretion and the proliferation of adrenocortical cells as autocrine and/or paracrine factor (pg 6, lines 23-25). SF06 is known in the art as cerebellin 2 precursor protein or precerebellin (Cbln2) (NM_172633; NM_182511; pg 40, Table 2). Applicant has found that SF06 is expressed in the pancreas (pg 11, lines 10-11; Figure 8).

However, the claims lack enablement because there are no working examples of the invention as claimed and the specification does not establish the necessary expression of a SF06 therapeutic protein alone or in combination with an SF06 gene therapy vector to achieve a clinically-meaningful result of a specific disease.

However, the claims lack enablement because there are no working examples disclosing teach how to make and use an enormous genus of SF06 peptides, variants or functional fragments thereof. There is insufficient guidance as to which amino acids to be altered, deleted, duplicated or added, and whether the resulting peptide maintains its structure and function(s) necessary to achieve a clinically meaningful result. The prior art recognizes that Cbln2 exerts a neuromodulatory function and thus are useful as a class of transneuronal regulators of synapse development and synaptic plasticity in various regions of the brain. However, the prior art is silent regarding SF06/Cbln2, or variants or fragments thereof, for the treatment of pancreatic diseases (e.g. diabetes mellitus, such as insulin dependent diabetes mellitus and/or non insulin dependent diabetes mellitus), obesity, metabolic syndrome, eating disorder, cachexia, hypertension, coronary heart disease, hypercholesterolemia (dyslipidemia), and/or gallstones, as contemplated by Applicant. The specification discloses no examples regarding which amino acids may be altered in the reference SF06 amino acid sequence so as to retain functionality so as to be useful in a therapeutic pharmaceutical composition to treat an enormous genus of etiologically and pathologically distinct diseases and/or disorders. The specification does not disclose any identifying characteristic as to how an artisan would have assayed functionality of the SF06 polypeptide variants as per the disclosed intended uses. The specification does not establish a biological and/or functional nexus between Cbln2 activity in the brain (prior art) and Applicant's contemplated Cbln2 activity in the pancreas. Such a nexus is absent in the prior art, and thus the artisan would be dependent upon the instant disclosure for instructions on how to make and use the enormous genus of SF06 polypeptides, variants and fragments thereof.

The specification is not enabled for such a broadly claimed invention. This is because there is a high degree of unpredictability associated with the use of the claimed embodiments, specifically the specification fails to teach which amino acids to be substituted, deleted or inserted, at which positions and in which combinations for a fragment of a SF06 protein or a

DNA encoding the same such that the protein fragment or the encoded protein fragment still possess the necessary activity. The unpredictability of the broadly claimed invention is further underscored by the absence of information concerning the stability and the proper folding for a functional fragment of SF06. In discussing peptide hormones, Rudinger has stated that "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study (Page 6, first sentence of Conclusions *In* J.A. Parsons, ed. "Peptide hormones", University Park Press, 1976). Furthermore, the relationship between the sequence of a peptide and its tertiary structure associated for its activity is not well understood and is not predictable (Ngo et al., *In* Merz et al., ed. "The protein folding problem and tertiary structure prediction", Birkhauser, 1994). The claimed SF06 variants could have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the polypeptide, as well as insertions and deletions. The specification and the claims do not place any limit on which amino acid to be subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. In addition, the specification do not place any limit on the number of amino acids that could be substituted. The specification and the claims do not provide any guidance as to which, or how many original amino acid(s) to be substituted, or to which type of substitution besides conservative substitution, or which amino acids could be deleted or inserted so that the claimed polypeptide could function as contemplated. No consensus sequence for the claimed polypeptides is disclosed in the specification.

One cannot extrapolate the teaching in the specification to the scope of the claims because one cannot predict that the SF06 variants would have properties related to that of the unadulterated SF06 amino acid sequence. It is well known in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology and that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. For example, Bowie et al (Science 257:1306-1310, 1990) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the

instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, pg 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, pg 1306). The 3-dimensional folding of the native molecule however is of significant importance in an antibody response, because epitopes of an antibody could be linear and/or conformational. The reference thus demonstrates that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the characteristics or three dimensional structure of a protein, and consequently the binding and characteristics of the antibodies specific for said protein. Thus one does not know how to make the SF06 variants such that they still have the function and properties of the wildtype SF06 polypeptide, and it would be undue experimentation for one of skill in the art to screen for the claimed variants.

Additionally, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Therefore, in the absence of sufficient guidance provided by the instant specification regarding to the use of any SF06 polypeptide or variant or fragment thereof to achieve a

clinically meaningful result for the treatment of an enormous genus of etiologically and pathologically distinct diseases and/or disorders would again require undue experimentation without a predictable expectation of success for a skilled artisan to make and use the instant broadly claimed invention.

The Level of One of Ordinary Skill, and The Level of Predictability in the Art

People of the ordinary skill in the art will be highly educated individuals such as medical doctors or scientists possessing advanced degrees, including M.D.'s and Ph.D.'s. Therefore, the level of ordinary skill in this art is high. However, the instant invention is drawn to a new use of an enormous genus of polypeptide variants. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to make and use the enormous genus of SF06 polypeptide variants for the treatment of pancreatic diseases (e.g. diabetes mellitus, such as insulin dependent diabetes mellitus and/or non insulin dependent diabetes mellitus), obesity, metabolic syndrome, eating disorder, cachexia, hypertension, coronary heart disease, hypercholesterolemia (dyslipidemia), and/or gallstones, as contemplated by Applicant because the biological role of SF06/Cbln2 in pancreatic development and/or disease etiology is unknown, and thus the artisan would have to invent for themselves assays by which to test which amino acids in SF06 may be altered, deleted, duplicated or added, and whether the resulting peptide maintains its structure and function(s) necessary to achieve a clinically meaningful result for the treatment, alleviation and/or prevention of pancreatic diseases such as diabetes, obesity, and other metabolic syndromes, and/or modulating pancreatic development and regenerating pancreatic tissues or cells.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the Applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the Applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. **Claims 1-22 are rejected under 35 U.S.C. 102(b)** as being anticipated by Barnes (WO 99/42576), as evidenced by Larsson et al (Scand. J. Immunol. 52:249-256, 2000).

With respect to claims 1, 3-4, 13, 21-22, Barnes discloses Cbln2 polypeptides and other compounds of the invention, e.g. Cbln2 encoding nucleic acids, that may be employed alone or in combination with other therapeutic compounds (pg 16, lines 16-17), wherein Cbln2 gene therapy treatment comprises the concomitant use of Cbln2 polypeptides, wherein the cells are then introduced into the subject (pg 17, lines 1-5). Barnes discloses mammalian Cbln2 polypeptides, and nucleic acid encoding said polypeptides, having at least 95%, 97%, 99% identity to SEQ ID NO:2 (human Cbln2), encoded by the nucleic acid of SEQ ID NO:1 (pg 2, lines 1-11).

With respect to claim 2, Barnes discloses the pharmaceutical formulations comprise pharmaceutically acceptable carriers (pg 16, lines 10-13).

With respect to claims 5 and 7-11, Barnes discloses the Cbln2-encoding nucleic acid may be a cDNA or genomic DNA (pg 5, lines 13 and 32-35), wherein the Cbln2-encoding nucleic acid is within a recombinant expression vector (pg 7, lines 16 and 28-34), wherein the recombinant Cbln2 polypeptide may be a fusion protein (pg 2, lines 29-33; pg 5, lines 17-24).

With respect to claims 6 and 13, Barnes discloses that the human Cbln2 polypeptide contributes to regulating metabolism (pg 14, lines 25-28).

With respect to claim 12, Barnes discloses a diagnostic composition comprising the inventive Cbln2 product(s) (pg 9, lines 23-33).

With respect to claims 14-20, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. The phrases "for…" are intended use limitations, which do not contain any further structural limitations with respect to claimed pharmaceutical composition comprising a SF06 protein and a SF06 nucleic acid (see MPEP §2114). While Barnes does not disclose the additional therapeutic agent to have immunosuppressive activity, those of ordinary skill in the art recognize that treatment modalities of Parkinson's disease (pg 14, line 25) may well comprise immunosuppression to promote the engraftment of neural xenografts (Larsson et al).

9. **Claims 1-22 are rejected under 35 U.S.C. 102(e)** as being anticipated by Hu et al (U.S. 2004/0248156 A1).

With respect to claims 1, 3-4, 6, 12-16, Hu et al disclose pharmaceutical compositions comprising polypeptides and nucleic acids encoding said polypeptides of the present invention, including Clbn2, may be involved in the generation or regeneration of other tissues, such as pancreas [0319]. C1q-related polypeptides and nucleic acids, e.g. Clbn2 [0007], will be advantageous to diagnose and treat a variety of disorders, including inflammation, immune disorders, diabetes and lipid metabolism [0011, 0214, 0390-391, 0411, 0417].

With respect to claim 2, the pharmaceutical compositions comprise an acceptable carrier [0018].

With respect to claims 5 and 7-11, Hu et al disclose the polynucleotide may be a cDNA or genomic DNA [0216] cloned into an expression vector [0016], and thus the Clbn2/SF06 polypeptide would inherently be a recombinant polypeptide, e.g. a fusion polypeptide [0225].

With respect to claims 17-20, Hu et al disclose the pharmaceutical composition may be used a monotherapy or combination therapy [0350-351] with additional agent(s) may have immunosuppressive activity.

With respect to claims 21 and 22, Hu et al disclose the pharmaceutical composition may be used *in vitro* or *in vivo* [0025, 0283].

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill, Ph.D./

Examiner, Art Unit 1633

/Q. JANICE LI, M.D./

Primary Examiner, Art Unit 1633